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Birth weight and risk of renal cell cancer

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Background. The prenatal period has been suggested to be important for future cancer risk. Conditions in utero are also important for the development of the kidney, and birth weight, a marker of fetal nutrition and growth, is linearly correlated with the number of nephrons and the structural and functional unit of the kidney. An association between birth weight and renal cell cancer, the major form of kidney cancer, is biologically plausible, but has never been studied.

Methods. We conducted a population-based, case-controlled study in Sweden of men and women aged 20 to 79 years. We collected self-reported information on categories of birth weight from 648 patients with newly diagnosed renal cell cancer and from 900 frequency-matched control subjects. We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) as estimates of the relative risks.

Results. An increased risk of renal cell cancer was observed among men with a birth weight of ≥3500 g (adjusted OR = 1.3, 95% CI, 1.0 to 1.8) compared with men with a birth weight between 3000 and 3499 g, especially in the subgroup without hypertension or diabetes (adjusted OR = 1.8, 95% CI, 1.2 to 2.6). No clear association among men with a birth weight <3000 g or among women was found.

Conclusions. Our study shows that conditions in utero, reflected by birth weight, might affect the risk of renal cell cancer in adulthood. It is unclear why no association was found among women. Further studies, based on weight from birth certificates, are needed to clarify this relationship.

The prenatal period has been suggested to be important for future cancer risk, and birth weight is often used as a marker of fetal nutrition and growth in such studies. High birth weight, indicating high levels of endogenous pregnancy hormones, has been associated with breast, prostate, and nonseminoma testicular cancer [1]. Low birth weight has been related to an increased risk of hypertension [2, 3] and non–insulin-dependent diabetes [3, 4], both associated with an increased risk of renal cell cancer [5–8]. Moreover, low birth weight has been related to an increased prevalence of overt albuminuria, a marker of renal disease [9]. Birth weight is linearly correlated to the number of nephrons, the structural and functional unit of the kidney [10]. An association between birth weight and renal cell cancer, the major form of kidney cancer, is therefore biologically plausible, but to our knowledge, this relationship has never been studied.

We evaluated the association between birth weight and risk of renal cell cancer in a large population-based, case-controlled study in Sweden.

Key words: kidney neoplasms, neonates and cancer risk, prenatal cancer risk, kidney cancer.

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METHODS

This was a population-based, case-controlled study of men and women aged 20 to 79 years, without previously diagnosed renal cell cancer, who were born in the Nordic countries and who resided in any of 19 counties in Sweden between January 1, 1996, and June 30, 1998. We identified all incident cases of renal cell cancer in this population through five of Sweden's six regional cancer registers. The patients were asked to participate in the study through their physicians. A total of 1275 eligible case subjects was detected from whom 877 (69%) participated in the study. Nonparticipation was due to death (12% of eligible cases), the patient being too ill or disabled (6%), or the patient refusing participation (13%). The cancer patients were contacted at least one month after diagnosis and on average after three months. All regional ethics committees and the Swedish Data Inspection Board approved the study protocol.

Control subjects were randomly selected from the continuously updated nationwide Swedish population register, frequency matched to the case patients by age (in 10-year strata) and sex. Of 2046 selected control subjects, 1508 (74%) agreed to participate in the study. Nonparticipation was mainly due to refusing participation (24% of selected control subjects).

All case and control subjects received a mailed self-administered questionnaire eliciting information on personal and medical history, including birth weight in five

predefined categories: <2500 g, 2500 to 2999 g, 3000 to 3499 g, 3500 to 3999 g, and ≥4000 g or "do not know." Because few persons reported a low (<2500 g) or high (≥4000) birth weight, the two categories of the lowest and the highest birth weight, respectively, were subsequently merged to increase statistical power. The questionnaire also covered information on education, cigarette smoking, usual adult weight, height, hypertension, and diabetes.

If needed, cases and control subjects were contacted by telephone to complete essential information missing in their responses. Among the controls, 284 failed to return the mailed questionnaire and were instead interviewed only by telephone. This short telephone interview did not include the question on birth weight.

The association between categories of birth weight and risk of renal cell cancer was measured using the odds ratio (OR) and its 95% confidence intervals (CI), computed from unconditional logistic regression models. Data were explored in models including only age (categorized as <40, 40 to 49, 50 to 59, 60 to 69, 70 to 79) as well as in models with age and the following covariates: education (<10, 10 to 12, >12 years), smoking (ever/never), usual body mass index (BMI = kg/m^2; divided into quartiles based on the distributions among control men and women separately), height (divided into quartiles based on the distributions among control men and women separately), hypertension (ever/never), and diabetes (ever/never).

RESULTS

A total of 648 cases of renal cell cancer and 900 control subjects reported their birth weight and were included in analyses. The distributions according to birth weight, age, education, smoking, usual adult BMI, height, hypertension, and diabetes among case and control subjects are shown in Table 1.

Case subjects with missing or unknown birth weight (N = 229) tended to be older than case subjects who reported their birth weight, while there was no difference in sex distribution. After adjustment for age and sex, they had lower education, were shorter, and suffered more often from hypertension. No difference was seen in the prevalence of smoking, BMI, or diabetes. Similarly, control subjects with a missing or unknown birth weight (N = 608) were older than the control subjects who reported their birth weight, but there were no differences in sex distribution. After adjustments for age and sex, they were less educated, smoked less, were shorter, and had a higher BMI. No difference was seen in the prevalence of hypertension or diabetes.

In age-adjusted models as well as in multivariate models further adjusting for education, smoking, normal adult BMI and height, an increased risk was observed among men with a birth weight of 3500 g and over compared with those with a birth weight between 3000 and 3499 g (Table 2). Further adjustments for hypertension and diabetes did not affect the estimates markedly (data not shown). There was no clear association between a birth weight below 3000 g and renal cell cancer risk among men. We found no clear association between birth weight and risk of renal cell cancer among women.

Low birth weight is associated with hypertension [2, 3] and non–insulin-dependent diabetes [3, 4], and both are associated with an increased risk of renal cell cancer [5–8]. Therefore, we investigated the association between birth weight and renal cell cancer in a subset of the study population without hypertension or diabetes. In this subsample, containing 380 case subjects (217 men

Table 1. Descriptive characteristics of renal cell cancer cases and control subjects included in the analyses of birth weight

	Men				Women			
	Cases (N = 378)		Controls (N = 544)		Cases (N = 270)		Controls (N = 356)	
	No	(%)	No	(%)	No	(%)	No	(%)
Birth weight *g*								
<2500	11	(3)	13	(2)	11	(4)	19	(5)
2500–2999	43	(11)	68	(13)	43	(16)	57	(16)
3000–3499	141	(37)	242	(44)	142	(53)	181	(51)
3500–3999	134	(35)	163	(30)	55	(20)	71	(19)
≥4000	49	(13)	58	(11)	19	(7)	28	(8)
Age *years*								
20–39	11	(2)	9	(2)	7	(3)	6	(2)
40–49	34	(9)	36	(7)	23	(9)	31	(9)
50–59	92	(24)	119	(22)	63	(23)	81	(23)
60–69	128	(34)	196	(36)	83	(31)	124	(35)
70–79	113	(30)	184	(34)	94	(35)	114	(32)
Education *years*								
<10	220	(58)	302	(56)	159	(60)	203	(58)
10–12	83	(22)	114	(21)	65	(24)	75	(21)
>12	75	(20)	122	(23)	43	(16)	75	(21)
Smoking								
Ever	237	(63)	335	(63)	130	(49)	137	(39)
Never	140	(37)	195	(37)	137	(51)	213	(61)
Usual adult BMI[a]								
Q1	88	(24)	132	(25)	46	(18)	93	(28)
Q2	82	(22)	140	(27)	55	(21)	90	(26)
Q3	74	(20)	132	(25)	64	(25)	83	(24)
Q4	130	(35)	123	(23)	93	(36)	74	(22)
Height[b]								
Q1	61	(16)	86	(16)	56	(21)	82	(23)
Q2	75	(20)	150	(28)	45	(17)	70	(20)
Q3	94	(25)	130	(24)	90	(33)	99	(28)
Q4	148	(39)	177	(32)	78	(29)	104	(29)
Hypertension								
Ever	144	(38)	129	(24)	100	(37)	81	(23)
Never	232	(62)	414	(76)	169	(63)	274	(77)
Diabetes								
Yes	47	(13)	33	(6)	28	(11)	15	(4)
No	328	(87)	511	(94)	238	(89)	338	(69)

[a]Usual adult BMI (kg/m^2). Among men: Q1, <22.72; Q2, 22.72–24.08; Q3, 24.09–25.34; Q4, ≥25.35. Among women: Q1, <21.26; Q2, 21.26–22.85; Q3, 22.85–24.61; Q4, ≥24.61.

[b]Height (meters). Among men: Q1, <1.72; Q2, 1.72–1.75; Q3, 1.76–1.79; Q4, ≥1.80. Among women: Q1, <1.60; Q2, 1.60–1.62; Q3, 1.63–1.67; Q4, ≥1.68.

Table 2. Odds ratio (OR) and 95% confidence interval (CI) of renal cell cancer in relation to categories of birth weight

	Men					Women				
		Model 1[a]		Model 2[b]			Model 1[a]		Model 2[b]	
Birth weight *g*	*N* of cases/controls	OR	95% CI	OR	95% CI	*N* of cases/controls	OR	95% CI	OR	95% CI
All										
<3000	54/81	1.1	0.8–1.7	1.2	0.8–1.8	54/76	0.9	0.6–1.4	1.0	0.6–1.5
3000–3499	141/242	1.0	Reference	1.0	Reference	142/181	1.0	Reference	1.0	Reference
≥3500	183/221	1.4	1.0–1.9	1.3	1.0–1.8	74/99	1.0	0.7–1.4	0.9	0.6–1.3
Without hypertension or diabetes										
<3000	32/57	1.5	0.9–2.5	1.6	0.9–2.8	40/50	1.3	0.8–2.1	1.3	0.8–2.3
3000–3499	68/174	1.0	Reference	1.0	Reference	83/132	1.0	Reference	1.0	Reference
≥3500	117/163	1.8	1.3–2.7	1.8	1.2–2.6	40/81	0.8	0.5–1.2	0.8	0.5–1.3

[a]Adjusted for age
[b]Adjusted for age, education, smoking, usual adult BMI, and height

and 163 women) and 657 control subjects (394 men and 263 women), a birth weight of 3500 g or more was associated with a significantly increased risk of renal cell cancer among men but not among women (Table 2). Furthermore, we observed a nonsignificant increased risk of renal cell cancer among men with a birth weight below 3000 g. The association among women was less clear. Because of the limited numbers, separate analyses on men and women with hypertension or diabetes were not meaningful.

DISCUSSION

In this population-based case-control study, which to our knowledge is the first to investigate the relationship between birth weight and renal cell cancer, an increased risk was observed among men with a high birth weight, while no clear association was found among men with a low birth weight. Among women, neither high nor low birth weight was clearly associated with risk of renal cell cancer. In a subset of men and women without hypertension or diabetes, the association between high birth weight and risk of renal cell cancer among men persisted, and low birth weight was suggested to increase the risk among men. Also here, we found no clear association between birth weight and renal cell cancer risk among women.

The major strength of our study includes its population-based design and the large number of cases. The Swedish regional cancer registers made it possible for us to ascertain virtually all incident cases of renal cell cancer, and the National population registry made it possible to select population controls.

One possible, but rather unlikely, limitation of our study is selection bias. Although a substantial number of the cancer patients (12%) died before they could be included or were too ill to participate (6%), this would influence our results only if birth weight is associated with short-term prognosis of renal cell cancer. Since we had no proxy interview information, we could not determine whether this unlikely bias was introduced. Refusing to participate in the study was more common among the control subjects, but it is unlikely that this would be associated with birth weight. Another concern is that only 74% (648) of the cases and 60% (900) of the control subjects answered the question on birth weight. This difference in response is partly due to the fact that the question on birth weight was not included in the short telephone interview with the 284 control subjects who failed to answer the mailed questionnaire. However, it is unlikely that nonresponse might be associated with birth weight. Therefore, selection bias probably has limited influence on our findings.

Misclassification of birth weight might have affected our results. Although birth weight was self-reported, validation studies demonstrate that it is reported reliably [11–13]. When self-reported birth weight was validated in an American population-based, case-controlled study of breast cancer, the Spearman correlation coefficient between self-reported category of birth weight and birth certificates was 0.83 for cases and 0.80 for controls [13]. This similarity in validity between cases and control subjects and the fact that birth weight is not a known risk factor for renal cell cancer make differential misclassification an unlikely explanation of our findings. Nondifferential misclassification caused by incorrect recalling of birth weight only leads to an underestimation of the true association [14].

An association between high birth weight and renal cell cancer is biologically plausible. Since birth weight is linearly correlated with the number of nephrons [10], subjects with a high birth weight will have a larger number of nephrons and thereby more cells at risk of malignant transformation.

Also, an association between low birth weight and renal cell cancer is biologically plausible. The total number of nephrons, the structural and functional unit of the kidney, is defined at birth, after which no new nephrons are formed [15]. Fetal growth retardation, marked by

low birth weight, leads to small kidneys with deficiency in nephron number [10, 15]. Recent evidence supports the view that deficits in nephron number indeed predispose to renal disease [16, 17]. A compensatory glomerular hypertrophy and hyperfiltration could result in glomerulosclerosis, which makes the nephrons more vulnerable for exposure to carcinogens.

Furthermore, low birth weight is associated with hypertension [2, 3] and non–insulin-dependent diabetes [3, 4], possibly due to changes in the concentrations of fetal and placental hormones caused by the fetus' adaptation to undernutrition [18]. Both hypertension and diabetes are associated with an increased risk of renal cell cancer [5–8] and could therefore be intermediate steps in an association between low birth weight and renal cell cancer. In our study, however, low birth weight was suggested to increase the risk of renal cell cancer among a subsample of men without hypertension or diabetes, indicating that there may also be some other mechanism involved.

In summary, our study shows that factors operating in utero, reflected by self-reported birth weight, might affect the risk of renal cell cancer in adulthood. It is unclear why no association was found among women. Further studies are needed to clarify the relationship between birth weight and risk of renal cell cancer. To exclude the effect of nondifferential misclassification on observed results, these studies should be based on actual birth weight, obtained from birth records. Furthermore, these studies should also take into account other prenatal and perinatal factors, such as gestational age, prepregnancy weight of the mother, weight gain during pregnancy, smoking during pregnancy, diseases such as diabetes, pre-eclampsia/eclampsia, and other indicators of pregnancy hormones or intrauterine factors.

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